510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k051757

B. Purpose for Submission:

Clearance to market a new Calcium Assay, Calcium-ADVANCE Assay, by Diagnostic Chemicals Ltd.

C. Measurand:

Total Calcium (Ca)

D. Type of Test:

Spectrophotometric

E. Applicant:

Diagnostic Chemicals Limited

F. Proprietary and Established Names:

Calcium-ADVANCE Assay

G. Regulatory Information:

1. Regulation section:

   21 CFR §862.1145 - Calcium test system.

2. Classification:

   Class II

3. Product code:

   CJY

4. Panel:

(75) Chemistry

H. Intended Use:

1. Intended use(s):

   A calcium test system is a device intended to measure total calcium in serum, plasma (Lithium Heparin), and urine. Calcium measurements are used in the diagnosis and treatment of hypercalcemia as a result from hyperparathyroidism, hypervitaminosisD, multiple myeloma, and some neoplastic diseases of the bones. It is also used in the diagnosis and treatment of hypocalcemia as a result from hypoparathyroidism, steatorreah, nephrosis, nephritis, and pancreatitis.

2. Indication(s) for use:

   "The Calcium-ADVANCE system is intended for the IN VITRO quantitative determination of total calcium in serum, plasma (Lithium Heparin), and urine. Calcium measurements are used in the diagnosis and treatment of hypercalcemia resulting from hyperparathyroidism, hypervitaminosisD, multiple myeloma, and some neoplastic diseases of the bones. It is also used in the diagnosis and treatment of hypocalcemia due to hypoparathyroidism, steatorreah, nephrosis, nephritis, and pancreatitis."

3. Special conditions for use statement(s):

   For Prescription Use only.

4. Special instrument requirements:

   None.

I. Device Description:

The Calcium-ADVANCE™ Reagent consists of a solution containing a buffer (pH 5.5 at 25°C), 60 µmol/L Phosphonazo III, stabilizers, and a preservative.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Cobas Ready Calcium Reagent

2. Predicate 510(k) number(s):

   k896224

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	IN VITRO quantitative determination of total calcium	IN VITRO quantitative determination of total calcium
Measurement Method	Spectrophotometric	Spectrophotometric
Sample Material	Serum, Urine, Plasma (Li-Heparin)	Serum, Urine, Plasma (Li-Heparin)
Format	Liquid, ready-to-use	Liquid, ready-to-use

Differences		
Item	Device	Predicate
Chromophore	Phosphonazo III	o-cresolphthalein complexone
pH	pH = 5.5	pH = 10.6
Storage Temperature	18-26°C	18-25°C
Linear Range	0.2 – 20 mg/dL Ca	0.2 – 16.8 mg/dL Ca

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP05-A2: Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline-Second Edition

CLSI EP06-A: Evaluation of the Linearity of Quantitative Analytical Methods; Approved Guideline

CLSI EP07-A: Interference Testing in Clinical Chemistry; Proposed Guideline

CLSI EP09-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Second Edition

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

L. Test Principle:

Phosphonazo III reacts with calcium in solution to form a blue-purple complex. The color developed has a maximum absorbance at 600 nm and is proportional to the

calcium concentration in the sample:

Phosphonazo III + Ca^{+2} → Ca-Phosphonazo Complex (blue-purple)

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Within run precision was assessed by measuring two levels of commercially available control sera, two levels of commercially available urine controls, and two concentrations of laboratory-prepared plasma. Each material was assayed 20 times:

Matrix	Conc. Level (mg/dL)	Standard Deviation (mg/dL)	CV(%)
Serum Control	9.0	0.05	0.5%
	11.9	0.06	0.5%
Urine Control	5.3	0.07	1.3%
	11.3	0.11	1.0%
Plasma	8.9	0.06	0.6%
	14.8	0.12	0.8%

   Between run precision was assessed by measuring two samples per run, two runs per day for twenty days for each matrix material:

Matrix	Conc. Level (mg/dL)	Standard Deviation (mg/dL)	CV(%)
Serum Control	9.0	0.11	1.2%
	12.1	0.17	1.4%
Urine Control	5.3	0.08	1.6%
	11.4	0.18	1.6%
Plasma	8.7	0.1	1.1%
	14.3	0.15	1.1%

   b. Linearity/assay reportable range:

   The linear range for this assay is 0.2 – 20 mg/dL Ca.

   The lower limit of the assay range was established following EP17-A. The company opted to apply a requirement of 3 standard deviations above their blank value as their lower limit of detection. This criterion corresponded to a concentration of 0.2 mg/dL total Ca.

To determine the upper limit of the linear range of this assay, the company used an Allowable Total Error of 1.0 mg/dL Ca, the HCFA limit for proficiency testing, and a systematic error budget of 33%. This gave an Allowable Systematic Error of 0.3 mg/dL. The residuals were calculated as the difference between the mean measured value and the estimated value obtained by linear regression. If the absolute value of the residual was less than the Allowable Systematic Error, the sample was considered to be within the linear range of the assay. The results of this analysis supported a linear range in excess of 20 mg/dL. The company rounded down to 20 mg/dL Ca as the upper limit of this assay.

For samples with concentrations above 20 mg/dL, the company recommends diluting the samples with saline.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

The stability (shelf life) of the reagent was determined from accelerated aging studies. Aging of the product at 37 °C for 7 days induced a 2.5% variance in the performance of the product. Aging of the product at 37 °C for 7 days, followed by subsequent storage at 50 °C for 7 days, induced at 2.7% variance in the performance of the product. These observations support the claimed shelf life of two years.

d. *Detection limit:*

The lower limit of the assay range was established following EP17-A. The company opted to apply a requirement of 3 standard deviations above their blank value as their lower limit of detection. This criterion corresponded to a concentration of 0.2 mg/dL total Ca.

e. *Analytical specificity:*

Interference studies were conducted according to CLSI EP07-A: Interference Testing in Clinical Chemistry; Proposed Guideline. Each potential interferent was tested once. At the concentrations in the table below the interferents induced less than a 10% variation in total Ca in urine, serum, and plasma samples in the clinically relevant concentration range.

Interfering Species	Concentration (mg/dL)
Lipemia	1000 mg/dL
Bilirubin	40 mg/dL
Hemoglobin	1000 mg/dL
Ascorbic Acid	3000 mg/dL

In addition, the company tested potential cation interference in serum, finding the cations in the table below would induce less than a 10% variation in total Ca for measurements made on samples in the clinically relevant concentration range:

Interfering Species	Concentration (mg/dL)
Cu^{+2}	6.4
Mn^{+2}	0.55
Mg^{+2}	12.6
Sr^{+2}	43.8
Zn^{+2}	0.65
MRI contrast agents	
Gadodiamide (Gd-DTPA-BMA)	14.4
Gadoversetamide (MP-1177)	16.5

Finally, the company demonstrated that the assay was linear in the presence of 6 g/dL Albumin following the procedure outlined in the "Linearity/assay reportable range", above.

The company determined that anti-coagulants that complex calcium – citric acid, oxalates, EDTA, and NaF – would interfere with this assay. These agents should not be used on samples intended for measurement with this device.

f. Assay cut-off:

Not applicable to this type of device.

2. Comparison studies:

a. Method comparison with predicate device:

The company followed CLSI EP09-A2: "Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline" in demonstrating their equivalence to their predicate.

In a comparison of the submitted device to the predicate using 125 clinical serum samples spanning the concentration range of the assay, the company showed:

Regression Analysis		
	Deming	Regular Least Squares
Slope	1.017 (1.008 – 1.025)	1.015 (1.006-1.023)
Intercept	-0.050(-0.071 - -0.029)	-0.045 (-0.066 - -0.024)
Standard Error Estimate	0.025	0.025

where the 95% confidence intervals are noted in parenthesis.

In a comparison of the submitted device to the predicate using 44 plasma samples obtained from patients, the company showed:

Regression Analysis		
	Deming	Regular Least Squares
Slope	0.971 (0.961 – 0.982)	0.971 (0.961-0.981)
Intercept	-0.001(-0.023 - 0.022)	0.000 (-0.022 - 0.023)
Standard Error Estimate	0.015	0.015

where the 95% confidence intervals are noted in parenthesis.

In a comparison of the submitted device to the predicate using 60 urine samples obtained from patients, the company showed:

Regression Analysis		
	Deming	Regular Least Squares
Slope	0.958 (0.946 – 0.971)	0.957 (0.945-0.970)
Intercept	0.343(0.189 - 0.496)	0.355 (0.201 - 0.508)
Standard Error Estimate	0.273	0.273

where the 95% confidence intervals are noted in parenthesis.

b. Matrix comparison:

Not applicable to this type of device.

3. Clinical studies:

a. Clinical Sensitivity:
Clinical studies are typically not required for this type of device.

b. Clinical specificity:
Clinical studies are typically not required for this type of device.

c. Other clinical supportive data (when a. and b. are not applicable):
Not applicable.

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

Serum[1]	
Premature Infants	6.0-10.0 mg/dL
Full-term infants	7.3-12.0 mg/dL
Child, 1 to 2 years	10.0-12.0 mg/dL
Adults	8.0-10.5 mg/dL
Plasma[2]	
Adults	8.6-10.3 mg/dL
Urine[*,1]	
Men	< 275 mg/24 hr
Women	< 250 mg/24 hr

*total output of calcium over a 24 hour period

[1] Kaplan, Lawrence A. and Pesce, Amadeo J., (Ed), Clinical Chemistry: Theory, Analysis, Correlation. Mosby-Year Book, Inc., St. Louis (1996).

[2] Burtis, C. A. and Ashwood, E. R. (Eds.) Tietz Textbook of Clinical Chemistry, W.B. Sounders Co., Philadelphia (1999)

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.